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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/450,999 11/29/99 PORTER

J CELL -0086

HM12/1201

EXAMINER

MCKENZIE, T

ART UNIT	PAPER NUMBER
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1624

14

DATE MAILED:

12/01/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/450,999	Applicant(s) PORTER ET AL.
	Examiner Thomas C McKenzie, Ph.D.	Art Unit 1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 25 September 2000.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 2-22 is/are pending in the application.
 - 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 2-22 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	18) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____
16) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	19) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
17) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>35789101</u>	20) <input type="checkbox"/> Other: _____

DETAILED ACTION

1. This action is in response to amendments filed 9/25/00. There are twenty-one pending claims. Claims 2-14 and 16 are compound claims. Claim 15 is a composition claim. Claims 17-22 are use claims. This is the second action on the merits. Claims 2-15 were previously rejected. Claims 16-22 are new. The Applications concerns β-amidobenzene propanoic acid compounds.

Information Disclosure Statement

2. The references of IDS #5, filed 1/14/00, have not been considered because they are all missing. The Examiner is particularly eager to see reference BS, listed on page 5 of the IDS.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating diseases, does not reasonably provide enablement for preventing any diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The

only established prophylactics are vaccines, not the β -amidobenzene propanoic acid compounds of the present application.

4. Claims 17 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating the diseases tabulated in claim 18, does not reasonably provide enablement for treatment of multiple sclerosis. Noseworthy's (Nature) review on treatment of MS lists "Adhesion-molecule signaling" in Table 2 on page A45 as a "Possible future therapeutic strategies". Thus, implying that such mechanistic approaches like Applicants have not demonstrated efficacy in MS. Noseworthy's (Curr. Opin. Neurology) second recent review on MS treatment describes adhesion molecules and MS in the paragraph spanning both column of page 289 and the following paragraph. An antibody to a4 integrins, which would have the same mechanism of action as Applicants' claimed molecules, is reported as "still under investigation." Again, implying that such approaches as Applicants' have not demonstrated efficacy in MS. Attention is drawn to the final two sentences of this passage "[t]his approach has also led to severe side effects ...".

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the last line of both claim 14 and claim 16, Applicants have the word "solvates". This reads on an unlimited and undefined number of solvent complexes with Applicants' claimed compounds.

What solvents are envisioned?

6. Claims 2-4, 7-13, and 15-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the fourth line from the end of claim 16, Applicants have the limitation "heteroatom-containing group." What is the structure of these possible groups? The claim language would read on an infinite number of groups of any size so long as one of the atoms therein was not carbon or hydrogen.

7. Claims 2-13 and 15-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants repeatedly claim "optionally substituted" in reference to their aliphatic, heterocycloaliphatic etc groups. This is indefinite because we do not know what these substituents are or where there are to be placed. The examiners suggests that these substituent

groups be spelled out in the claims so that we know what Applicants intend. For example, in the lines spanning pages 3 and 4 of the amendments Applicants do definitely claim what they intend for R^b.

Applicants have argued that improved definition of the size of the aliphatic, heterocycloaliphatic etc groups makes "further explanation unnecessary". This is not persuasive. This rejection is not about the groups (but please see the point below) but the identity of the substituents.

8. Claims 2-13 and 15-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claim 16, Applicants repeatedly refer to "heteroatoms", "heteroaromatic", and "heteroaliphatic". Beyond the fact, these various heteros are not carbon or hydrogen atoms, Applicants have not told us what atoms are contemplated. Hetero might be limited to nitrogen and sulfur atoms only. It might include the nitrogen, sulfur, and oxygen atoms of Applicants' working examples. It might include some or all of the remaining 113 atoms in the periodic table. Does hetero include a uranium atom or a chlorine atom, for example?

9. Claims 2-13 and 15-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the

Art Unit: 1624

subject matter which applicant regards as the invention. In claim 16, Applicants repeatedly refer to "heteroaliphatic", "cycloaliphatic", and "polycycloaliphatic" and "hetero polycycloaliphatic". These are all improper. To quote from Hawley (The Condensed Chemical Dictionary) "aliphatic ... characterized by straight- or branched-chain arrangement of the constituent carbon atoms." An aliphatic group may be saturated or unsaturated. An aliphatic group may not contain rings or hetero atoms. Applicants terms "heteroaliphatic", "cycloaliphatic", and "polycycloaliphatic" and "hetero polycycloaliphatic" are not recognized in the art of organic chemistry and are oxymorons. Thus, we do not know what Applicants intends. The Examiner suggests "alicyclic" and "heterocyclic" if that is what they intend.

The term "heteroaliphatic containing one, two, three, or four heteroatoms" is particularly troublesome. We do not know what atoms are meant by hetero nor do we know where in the chain they are placed. Do the the hetero atoms interrupt the chain or are they substituents on the chain? If the hetero atom is oxygen, do Applicants intend a hydroxyl substituent on a carbon chain or might it mean four contiguous oxygen atoms followed by a carbon atom. Alkoxy and $-NR^dR^e$ substituents on an aliphatic chain would embrace what Applicants appear to intend.

10. Claims 2-13 and 15-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claim 16, Applicants have amended the words "carboxylic acid, or an ester or amide". This does clarify what they intended by "acid derivative". Unfortunately, the words "carboxylic acid, or an ester or amide" are all compounds not radicals, i.e. molecules with completely satisfied valences. The Examiner suggests 'carboxyl, carbonylalkoxy, or carboxyamido'.

11. Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "a disease or disorder in a mammal in which the extravascation of leukocytes plays a role" is indefinite. How large must this role be to qualify a disease under this claim? The claims provide for the use of the compounds of claim 16, but the claim does not set forth any steps involved in determining how to identify "a disease or disorder in a mammal in which the extravascation of leukocytes plays a role". It is unclear what diseases and treatments applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how to practice this use. Identifying those diseases applicants intend this claim to cover will

involve extensive and potentially inconclusive clinical research. Without such clinical research to identify the patients and diseases applicants intend to treat, one skilled in the art cannot determine the metes and bounds of the claim. Hence, the claims are indefinite.

Claim Rejections - 35 USC § 101

12. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

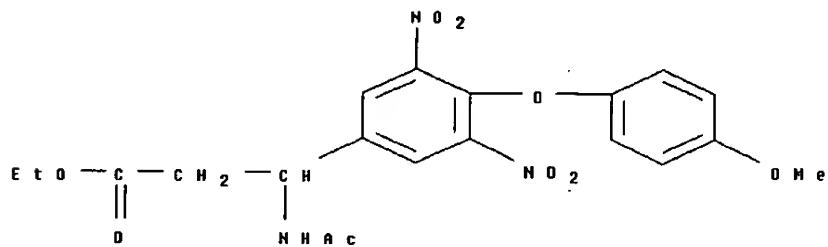
Claims 21 and 22 rejected under 35 U.S.C. 101 because neither a specific nor substantial asserted utility nor a well-established utility supports the claimed invention. The rejected claims are not drawn to the treatment of a disease, neither generally nor specifically, and there is no data in the record that compounds, which inhibit $\alpha 4$ binding, have successfully treated any disease. What is the purpose of "inhibiting, in a mammal, the binding of $\alpha 4$ integrins to the ligands thereof, [with] a compound of claim 16"? Note, the credibility of Applicants' claimed utility could not be assessed.

Claims 21 and 22 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth

above, one skilled in the art clearly would not know how to use the claimed invention.

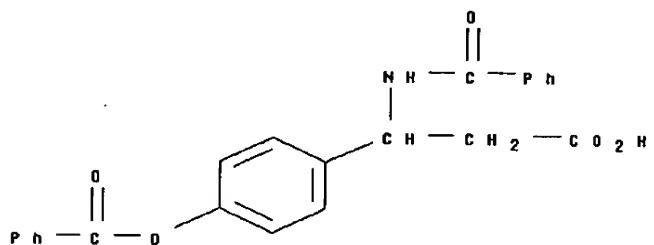
Claim Rejections - 35 USC § 102

13. Claims 3, 4, 7, 9, 10, 12, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Suvorov (Zhur.Obsh.Khim.). Two compounds in this reference anticipated Applicants' claims with $\text{Ar}^1 = \text{p-methoxyphenyl}$, $r = 0$, $L^1 = -\text{O}-$ and $-\text{S}(\text{O})_2-$, $\text{Ar}^2 = 3,5\text{-dinitro-1,4-phenylene}$ and $3,5\text{-iodo-1,4-phenylene}$, $R^1 = \text{NHC(O)CH}_3$, $R^a = R^{a'} = \text{hydrogen}$, and $R = \text{CO}_2\text{ethyl}$. The former compound is shown below is found in lines 6-7 of paragraph 6431e. The latter may be found in lines 2-3 of paragraph 6431f.

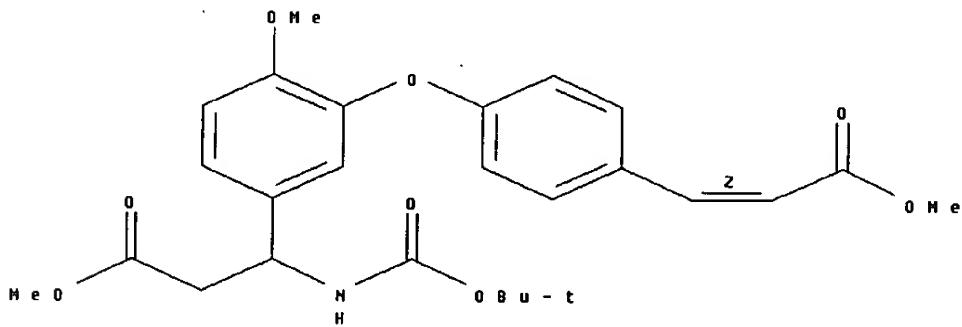


14. Claims 2-4, 7-9, 10, 12, 13, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Rodionov (Zhur.Obsh.Khim.). The compound shown below anticipated Applicants' claims with $\text{Ar}^1 = \text{phenyl}$, $r = 0$, $L^1 = -\text{C}(\text{O})-\text{O}-$, $\text{Ar}^2 = -1,4\text{-phenylene}$, $R^1 = \text{NHC(O)phenyl}$, $R^a = R^{a'} = \text{hydrogen}$, and $R = \text{CO}_2\text{H}$. The

compound is found in the last line of paragraph 6260c of the abstract "the O,N-dibenzoyl deriv."



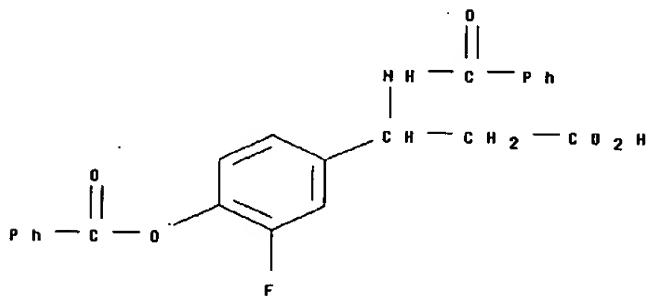
15. Claims 3, 4, 7, 9, 10, 12, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Wasserman (JACS). The compound shown below anticipated Applicants' claims with Ar¹ = 4-(3-methoxy-3-oxo-1-propenyl)phenyl, r = 0, L¹ = -O-, Ar² = 4-methoxy-1,4-phenylene, R¹ = NHC(O)OBu^t, R^a = R^{a'} = hydrogen, and R = CO₂methyl. Compound 22 is found in Scheme III on page 1698.



16. Claims 2-4, 7, 9, 10, 12, 13, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Mamaev (Zh.Obshch.Khim.). The compound shown below anticipated Applicants' claims with Ar¹ = phenyl, r = 0, L¹ = -C(O)-O-, Ar² = 3-

fluoro-1,4-phenylene, $R^1 = \text{NHC(O)phenyl}$, $R^a = R^{a'} = \text{hydrogen}$, and $R = \text{CO}_2\text{H}$.

The compound is found in the last two lines of the abstract 2748e, "O,N-diBz deriv.".



Response to Amendment

17. Applicants amendment limiting the size of the cycloaliphatic, heteroaromatic, heterocycloaliphatic etc groups, while not directly addressing the rejection made previously concerning the number of ring contained in these groups, does so indirectly. We may assume that a "C₇₋₁₀heteropolycycloaliphatic" group contains no more than five to eight rings for example.

Conclusion

18. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mukund Shah can be reached on (703)

308-4716. The fax number for the organization where this application has been assigned is (703) 308-4556. Please direct any inquiry of a general nature or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Mukund J. Shah
Mukund Shah
Supervisory Patent Examiner
Art Unit 1624

TCMcK *TCh*
November 30, 2000